SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SCHIFF BASE COMPLEXES OF TIN, SILICON, LEAD AND ZIRCONIUM

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1. INTRODUCTION

Recent developments in inorganic and organometallic have resulted in a very significantly increased understanding of the bonding structure and reactivity of coordination chemistry. Equally however, the border area between inorganic chemistry and life science should present a challenge to the inorganic chemist to apply his increased understanding in the design of model systems that throw light on behavior of metal ion in biological process and ultimately to look more closely at these process themselves.

Coordination chemistry is one of the most active fields of research in the area of inorganic chemistry. The use of coordination compounds as biological probes present as one of the most successful application of the bioinorganic chemistry. The transition as well as nontransition metallic elements have unparallel tendency to form coordination compounds with Lewis bases. The chemistry of these complexes with Schiff bases continues to attract many researchers, because of their wide applications in food industries, dye industries and in analytical chemistry as well as catalysis[1] and herbicides[2]. These complexes also show higher nematicidal and insecticidal properties[3].

Schiff bases are an important class of compounds in medicinal and pharmaceutical field. Schiff base constitutes one of the most important classes of biologically active ligands providing potential binding sites through N and S/O atoms. Schiff base metal complexes have played a major role in the development of coordination chemistry. The metal thiosemicarbazones or semicarbazones also have been found to possess significant biological and pharmacological activities[4] and may be used as fungicides, bactericides and antitumor agents.

There are enough possibilities of the studies on N and S/O donor systems due to their biochemical properties e.g. nitrogen and S/O donor ligands possess a range of applied applications like antiviral[5], antitubercular, antibacterial[6], antifungal[7], anthelmentic[8] and antimicrobial[9] agents as well as their antifertility[10] activity. Schiff bases containing polyfunctional groups have not only produced stable complexes of transition metals but these ligands and their metal complexes have also played a significant role in domains of stereochemistry, kinetics and mechanism of reactions,electro-optical display devices and agriculture.

Many biologically important Schiff bases have been reported in the literature possessing, antimicrobial, antibacterial, antifungal, anti-inflammatory, anticonvulsant, antitumor and anti HIV activities[11-16]. Another important role of Schiff base structure is in transamination[17]. Transamination reactions are catalyzed by a class of enzymes called transaminases. Transaminases are found in mitochondria and cytosal of eukaryotic cells. All the transaminases appear to have the same prosthetic group, i.e., pyridoxal phosphate, which is covalently attached to them via an imino group. Schiff base formation is also involved in the chemistry of vision, where the reaction occurs between the aldehyde function of 11-*cis*-retinal and amino group of the protein (opsin)[18]. The biosynthesis of porphyrin, for which glycine is a precursor, is another important pathway, which involves the intermediate formation of Schiff base between keto group of one molecule of δ-aminolevulinic acid and ε-amino group of lysine residue of an enzyme.

Transition metals are known to form Schiff base complexes and Schiff bases have often been used as chelating ligands in the field of coordination chemistry. Their metal complexes have been of great interest for many years. It is well known that N and S atoms play a key role in the coordination of metals at the active sites of numerous metallobiomolecules[19]. Schiff base metal complexes have been widely studied because they have industrial, antifungal, antibacterial, anticancer, antiviral and herbicidal applications[20-25]. They serve as models for biologically important species and find applications in biomimetic catalytic reactions. Chelating ligands containing N, S and O donor atoms show broad biological activity and are of special interest because of the variety of ways in which they are bonded to metal ions. It is known that the existence of metal ions bonded to biologically active compounds may enhance their activities[23-28].

Transition and non-transition metal complexes in (O_4)[29], (S_2N_2)[30], (S_4)[31], (N_3O)[32] and (N_2O_2)[33] coordination environment ligands other than chalcone derivatives have been proposed as possible adjunct in the treatment of diabetes mellitus (a dieses of carbohydrate metabolism due to inadequate production or utilization of insulin characterized by hyperglycemia). Vanadium is arguably the most thoroughly studied and efficacious insulin enhancing transition metal; a wide variety of tin and platinum containing complexes have been tested as anti-tumor agents. Whether tin and platinum containing might be unique among metal ions in this regards has not been addressed systematically[34].

The continuing interest in the multi dentate chelating agents with nitrogen, sulfur and oxygen as donor atoms and their metal complexes has been stimulated by a number of factors such as their interesting and very often unique stereo chemical features, widespread occurrence in living matter and many other practical applications as reflected by the large

number of citations in the literature[35-45]. These are frequently used as antimicrobial, anti cancerous, anti-tumor, antipyretic and ant tuberculosis agents.

2. OBJECTIVES

For educational, economic, environmental and social reasons, the trend toward the design, synthesis, characterization and application of chemical compounds is undoubtedly increasing. Especially the synthesis of biologically active compounds such as pharmaceuticals, agrochemicals, flavors and fragrances as well as creation of advanced materials have got great attention. Chemists in their research or project work are thus, usually interested in synthesizing, isolating, identifying, studying properties and applications of chemical compounds.

2.1 General Objectives

The general objectives are the following.

- Develop the skill of independent laboratory work
- Develop experience of how to handle and use chemicals.
- Develop the skill of synthesis, separation (purification) of compounds and then further characterizing those using analytical and spectral methods.
- Acquire knowledge of how to deal with the research or project work

2.2 Specific Objectives

- Synthesis and purification of biological important ligands and their Sn, Si, Pb and Zr complexes
- Characterization of these compounds (eg., melting point, conductance, elemental/thermal analysis, IR, NMR, etc.
- Interpretation of physical datas, like IR, NMR, UV, etc.
- Explanation of their properties and applications.
- Elucidation of structural formula on the basis of interpretation of physiochemical data and theoretical explanations from the literature surveys.
- Investigation of Antimicrobial activity.

3. LITERATURE REVIEW

3.1 Schiff base ligands

Schiff base was first reported by Hugo Schiff in 1864.[46] Schiff bases can be prepared by condensing carbonyl compounds and amines in different conditions and in different

solvents with the elimination of water molecules. The presence of a dehydrating agent normally favours the formation of Schiff bases. Though the Schiff bases are stable solids, care should be taken in the purification steps as it undergoes degradation. Chromatographic purification of Schiff bases on silica gel is not recommended as they undergo hydrolysis. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R', where R and R' are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. Presence of a lone pair of electrons in an sp2 hybridised orbital of nitrogen atom of the azomethine group is of considerable chemical importance and impart excellent chelating ability especially when used in combination with one or more donor atoms close to the azomethine group. Examples of a few compounds are given in Figure. This chelating ability of the Schiff bases combined with the ease of preparation and flexibility in varying the chemical environment about the C=N group makes it an interesting ligand in coordination chemistry.

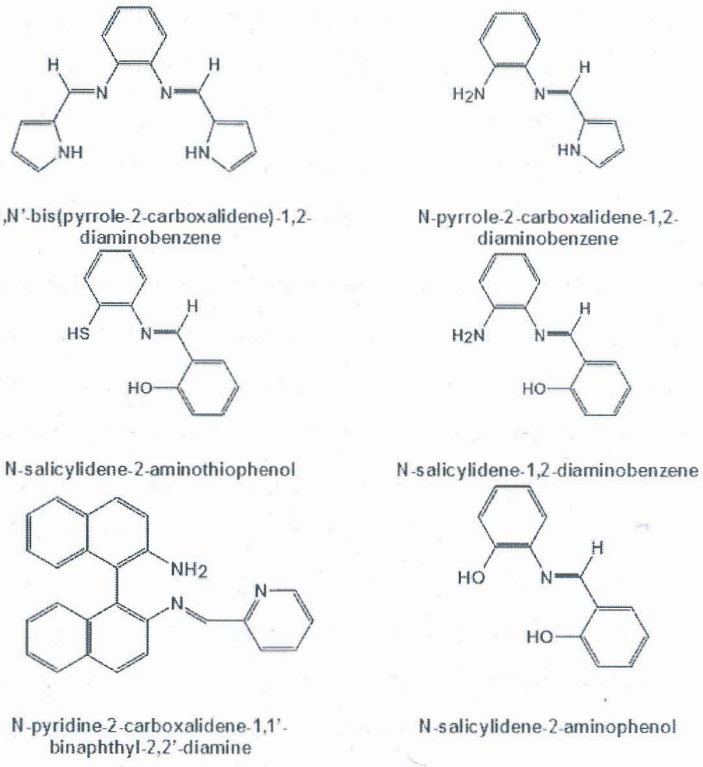


Figure: Some examples of Schiff bases

3.2 Schiff Base as Coordinating Ligands

Schiff base ligands coordinate to a metal through the imine nitrogen and another group, usually oxygen, situated on the original aldehyde. When a diamine was first combined

with two equivalence of salicylaldehyde, the ligands came into being. The ligands feature two covalent and two coordinate covalent sites situated in a planar array. This makes the ligands ideal for the equatorial coordination of transition metals, leaving the two axial sites open for ancillary ligands. They are very much like porphyrins in this regard, but unlike porphyrins the Schiff base ligands are easy to prepare and are relatively inexpensive. Schiff bases are among the most general N ligands, because the basicity of the sp^2-hybridized N lone pair, although lower than that of amines (sp^3 hybridization), is well suited to form complexes with metal ions. The salicylidene imine group is prone to undergo an acid-catalyzed hydrolysis, reverting to the corresponding salicylaldehyde and diamine in the presence of water. However, the stability of the Schiff base group increases considerably upon coordination with a metal ion and formation of the Schiff base-metal complex. For this reason, in contrast to the free ligand, the Schiff base-metal complex can be used in wet solvents or even in aqueous media without undergoing hydrolysis[47] (Baleizao and Gracia, 2006). Evidence for the tremendous amount of transition-metal chemistry that has been conducted is demonstrated by the fact that the first review in this area was published in 1966 (Holm *et al.*,)[48]. By incorporating additional groups around the phenol portion of the ligand, such as *tert*-Butyl, the ligands can be made highly soluble in aromatic and aliphatic solvents. Incorporation of hydrophilic groups may also lead to ligands that are soluble in water and alcohols[49].

3.3 Applications of Schiff Bases and Their complexes

Schiff bases and their complexes have a wide variety of applications. They are useful in biological field, as anticancer[50], as antitumor[51], as antituberculous[52], as antimalaria[53-55] and also they are found to have clinical, therapeutic[56] and analytical applications[57]. Earlier work has shown that some drugs showed increased activity when administered as metal chelates rather than organic compound[58].

The malleability inherent to the Schiff base ligands has led to their extensive use in transition-metal chemistry, particularly in modeling enzymes and in catalysis[59]. Schiff bases are suitable ligands for the preparation of libraries due to the easy reaction conditions. Variety of chiral amines and aldehydes are used as precursors to synthesize Schiff bases. Amino acids and peptides are particularly suitable for the creation of effective catalysts. The condensation of aldehyde-bearing coordinating groups with amino acids and peptides provide interesting Schiff bases, used to make a combinatorial library of ligands[60].

3.4 In medicinal chemistry

Many Schiff bases are known to be medicinally important and used to design medicinal compounds[61-64]. It was seen that the biological activity of Schiff bases either

increase or decrease upon chelation with metal ions[65-67]. Cobalt(II), nickel(II) and copper(II) complexes of Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazole and 8-formyl-7-hydroxy-4- methylcoumarin show potent antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Salmonella typhi* and antifungal activities against *Aspergillus niger*, *Aspergillus flavus* and *Cladosporium*[68]. Ru(II)–PPh3/AsPh3 complexes, containing hydrazone oxime ligands, show considerable activity against selected bacterial species and are capable of binding to Herring sperm DNA in mixed modes[69]. The Cr(III), Fe(III) and Co(III) complexes formed form tetradentate (ONNO) Schiff base ligands, 1,4-bis[3-(2-hydroxy-1-naphthaldimine)propyl]piperazine and 1,8-bis[3-(2-hydroxy-1-naphthaldimine)-*p*menthane, show moderate antimicrobial activity[70] compared to standard antibiotics[71]. The antibacterial activity of the tridentate Schiff base, formed by condensation of 2-amino-3-carboxyethyl-4,5-dimethylthiophene with salicylaldehyde, was found to increase on chelation with transition metal ions[72]. Co(II), Ni(II), Cu(II) and Zn(II) complexes of the Schiff base derived from vanillin and DL-α-aminobutyric acid were also found to exhibit higher antibacterial activity compared to the free Schiff bases[73]. Several mono and binuclear transition metal complexes of the Schiff base derived from phenylaminoacetohydrazide and dibenzoylmethane, are more potent bactericides and fungicides than the ligand[74]. Sharma and Piwnica-Worms reported Schiff base complexes that target hemozoin aggregation like the antimalarial drug, chloroquine[75-77].

Investigations on the interactions of DNA with transition metal complexes provide leads for rational drug design, as well as means for the development of sensitive chemical probes for DNA[78-90]. These interactions would be either covalent or non-covalent. In covalent binding the labile part of the complexes is replaced by a nitrogen base of DNA. On the other hand, the non-covalent DNA interactions include intercalative, electrostatic and groove binding of cationic metal complexes along periphery of the DNA helix, the major or minor groove. Intercalation involves the partial insertion of aromatic heterocyclic rings between the DNA base pairs.

4. Plan of research work and methodology

In order to achieve the objectives mentioned above the present study would be carried out in the following phases, keeping the above background knowledge in view:

(a) Starting materials of Tin, Lead, Silicon and Zirconium will be synthesized or purchased. Synthesis of metal precursors, if not available commercially.

(b) Synthesis of Schiff bases.

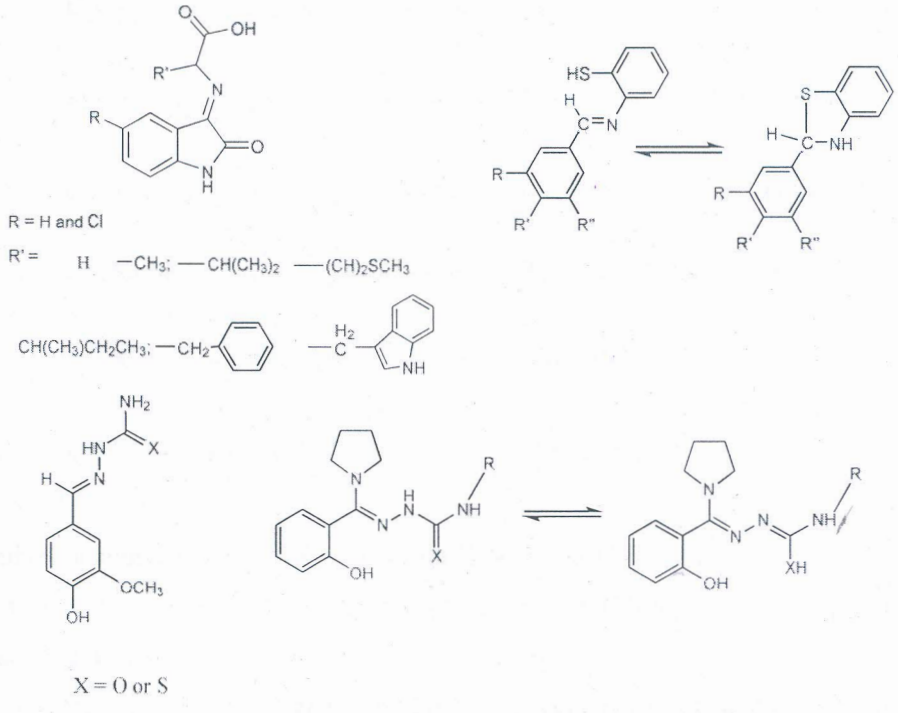
(c) Synthesis of metal complexes involving Schiff bases

(d) Characterization of complexes by analytical and Spectroscopic technique.

(e) Antimicrobial activity.

During the present investigations complexes of Sn(II), Pb(II), Sn(IV), Si(IV) and Zr(IV) with Schiff bases will be synthesized and the work will be carried out on the following lines:

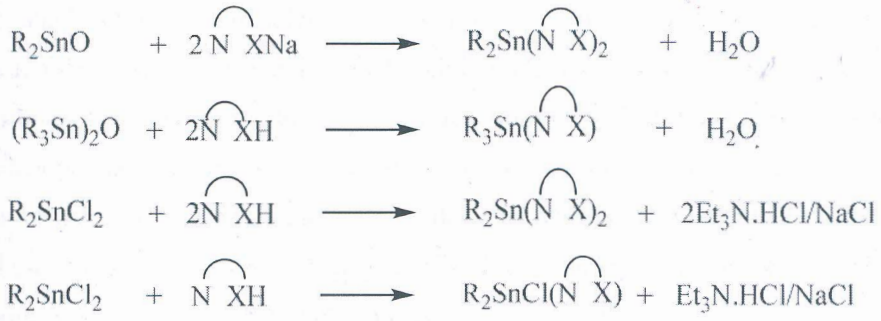
(1) Synthesis of Ligands: Ligands which are of stereo chemical as well as biochemical significance containing nitrogen, oxygen and sulphur donor atoms will be synthesized. They will include Schiff bases of amino acids, semicarbazones, thiosemicarbazones and benzothiozolines.



(2) Reactions of Sn(II), Pb(II), Sn(IV), Si(IV) and Zr(IV) salts with Ligands such as monofunctional bidentate, bifunctional tridentate Schiff bases derived from amino acids, will be carried out.

The different molar reactions of acetates and halides derivatives of tin, lead, titanium, and zirconium metals with the Schiff base of stereo chemical as well as biochemical significance will be investigated. The resulting derivatives will be isolated I a stage of

efficient purity then systematically examined. The proposed few representative reactions and structures for tin are as follows: -



(3) Similar reactions of metal salts with benzothizolines will be carried out.

(4) These reactions will result in the formation of metal complexes of Schiff bases containing nitrogen, oxygen and sulphur donor atoms.

(5) These complexes will be isolated and purified by recrystallization and their elemental analyses will be carried out.

(6) Molar conductances in suitable solvents will be measured to determine the electrolytic nature of the complexes.

(7) IR spectra will be recorded and the absorption bands will be assigned to vibrations of different bonds.

(8) UV/VIS spectra will be recorded and the absorption bands will be assigned to various electronic transitions.

(9) 1D and 2D NMR spectra of the complexes will be recorded and will be interpreted to elucidate the structures of the complexes.

(10) DFT and semi-empirical calculations will be carried out by a program such as gaussion 03 which is a general purpose semi-empirical molecular-orbital package for the study of chemical structures and the reactions. Using B3LYP methods various parameters such as heats of formation, bond lengths, bond angles, ionization potentials, atomic charges, atom electron densities will be determined. With the help of these parameters optimized geometries of the complexes will be worked out. Determination of the unit cell parameters, crystal orientation, if determined.

(11) The representative derivatives will be subjected to biochemical studies such as antifungal, antibacterial and anticancer in collaboration with research institutions/research laboratories where such facilities are available.

5. WORK ALREADY DONE

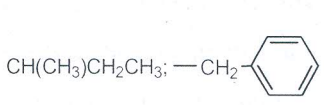
5.1 Investigation of the reaction of isatin and substituted isatin with various amino acids.

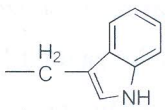
5.1.1 Synthesis of monofunctional bidentate Schiff bases.

The ligends were synthesized by the condensation of isatin , 5-chloroisatin, with the amino acids in 1:1 molar ratio using methanol as the reaction medium and were then, it was refluxed for 4-5 h. After this it was put on cooling at room temperature and the solid products were obtained. The excess solvent was removed on a rotary evaporator. It was further dried and then purified by recrystallization from same solvent.

R = H and Cl

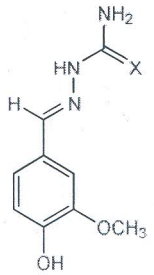
R' = H —CH_3; —$CH(CH_3)_2$ —$(CH)_2SCH_3$





5.1.2 Synthesis of monofunctional bidentate Ligands.

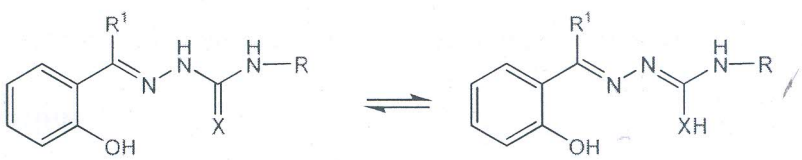
The ligends were synthesized by the condensation of 4-hydroxy-3-methoxybenzaldehyde, with semicarbazide, thiosemicabazide in 1:1 molar ratio using ethanol as the reaction medium and were then, it was refluxed. After this it was put on cooling at room temperature and the solid products were obtained.



X = O or S

5.1.3 Synthesis of bifunctional tridentate Ligands.

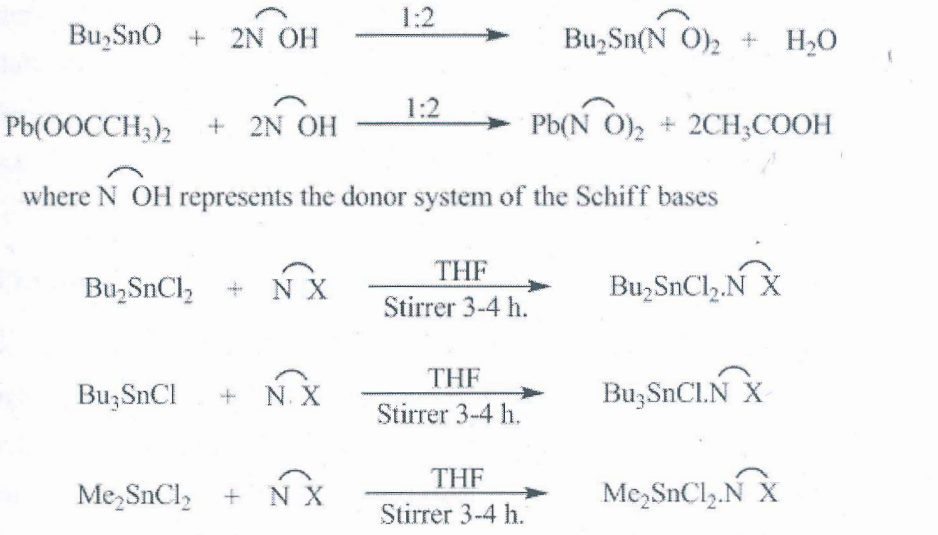
The ligends were synthesized by the condensation of 3-hydroxy-2-methyl-4-pyrone, N-2-hydroxy benzene pyrolidine, with semicarbazide, thiosemicabazide, substituted thiosemicarbazone in 1:1 molar ratio using ethanol as the reaction medium and were then, it was refluxed. After this it was put on cooling at room temperature and the solid products were obtained.



R = H or C_6H_5; X = O or S and $R^1 = C_4H_8N$

5.2 Synthesis of Metal Complexes

New metal complexes were synthesized by the reaction of dibutyltin(IV) oxide and lead(II) acetate with monofunctional bidentate Ligands have been carried out in 1:2 molar ratios using anhydrous benzene and absolute methanol in 3:1 ratio as solvent. These reactions proceed with the liberation of water and acetic acid. The scheme of the Organotin(IV) and lead(II) complexes preparation is given by Scheme 1.


Bu2SnO + 2N OH 1:2 Bu2Sn(N O)2 + H2O
Pb(OOCCH3)2 + 2N OH 1:2 Pb(N O)2 + 2CH3COOH
where N OH represents the donor system of the Schiff bases
Bu2SnCl2 + N X THF Stirrer 3-4 h. Bu2SnCl2.N X
Bu3SnCl + N X THF Stirrer 3-4 h. Bu3SnCl.N X
Me2SnCl2 + N X THF Stirrer 3-4 h. Me2SnCl2.N X
where N X represents the thiosemicarbazone/semicarbazone and X = Sulfur/Oxygen

Scheme 1 Representative equation illustrating the formation of Organotin(IV) complexes

These New Schiff base ligands, which are not commercially available have been synthesised by the condensation of aromatic aldehydes or ketones with semicarbazide hydrochloride and thiosemicarbazide. Ligands thus synthesised are being characterised elemental analysis and spectroscopic (IR, UV, NMR) spectral data. Same representative ligands in each category have been synthesized and characterized and the synthesis of analogous ligands having different substituents are in progress. Few representative ligands and metal complexes have also been screened for their antifungal and antibacterial activities.

6. Work Output

The following series have been completed and published in the International Journal of Chemistry.

Paper published in Journal

1. Synthetic, structural, and antimicrobial studies of organotin(IV) complexes of semicarbazone,thiosemicarbazone derived from 4-hydroxy-3-methoxybenzaldehyde, Res. Chem. Intermed. **38**:53-65 (2012), Publisher: Springer, USA.
2. Synthesis and characterization of new lead(II) and organotin(IV) complexes of Schiff bases derived from histidine and methionine. (International journal of inorganic chemistry) Volume 2012 Article ID 568797, pages 1-7. Publisher: Hindawi Publishing Corporation, USA.

3. Synthesis, spectral, 3D molecular modeling and antibacterial studies of dibutyltin (IV) Schiff base complexes derived from substituted isatin and amino acids Natural Science Vol.4, No.3, 170-178 (2012). Publisher: Scientific Research Publishing, USA.

7. CONCLUSIONS

The newly synthesized Schiff bases act as bidentate ligands coordinating to metal ions through azomethine nitrogen, thionic sulphur, and ketonic oxygen atoms. Square planer and octahedral geometries have been proposed for metal complexes with the help of different spectral studies like IR, UV, 1H, 13C, and 119Sn NMR. The Schiff bases and their metal complexes were found to be highly active against some of the antibacterial and antifungal species. The activity is significantly increased on coordination.

8. References:

1. M. Bochmann, *J. Chem. Soc., DaltonTrans.*, 255(1996).
2. A. Abarca, P.Gomez-Sal, A.Martin, M.Mena, J.M.Poblet, C.Yelamos, *Inorg. Chem.*,39, 42(2000).
3. M.Saiz, T.Cuenca, M.Galakhov, A.Grassi, R.K.J.Bott, D.L.Hughes, S.J.Lancaster, M.Bochmann, *Organo-metallics*, 23, 5324(2004).
4. S.K.Mandal, P.M.Gurubasavraj, H.W.Roesky, G.Schwab, D.Stalke, R.B.Oswald, V.Dolle, *Inorg. Chem.*, 46, 10158(2007).
5. P.K.Maier, B.Hesse H.Kopf, *J. Cancer Res. Clin. Oncol.*, 96, 43(1980).
6. M.Guo, H.Sun, S.Bihari, J.A. Parkinson, R.O.Gould, S.Parsons, P.J.Sadler, *J. Inorg. Chem.*, 39, 206(2000).
7. G.Kelter, N.J.Sweeney, K.Strohfeldt, H.H.Fiebig, M.Tacke, *Anti Cancer Drugs*, 16, 1091(2005).
8. I.Fichtner, C. Pampillon, N.J.Sweeney, K.Strohfeldt, M.Tacke, *Anti Cancer Drugs*, 17, 333 (2006).
9. H L Singh, Spectrochimica Acta P-A, 76, 253 (2010).
10. S.Sinha, A.K.Srivastva, C.M.Tripathi, O.P.Pandey, S.K.Sengupta, *Bioinorg. Chem. Applic.*, 2007(2007).
11. M. Nath, H. Singh, G. Eng, X. Song, X. *Inorganic Chemistry Communications*, **14**, 1381-1385. doi:10.1016/j.inoche.2011.05.027 (2011).
12. S.N. Pandeya, D. Sriram, G. Nath, E. de Clercq, *Arzneimittel Forsch.* 50, 55 (2000).

13. X. Ran, L. Wang, D. Cao, Y. Lin, J. Hao, *Applied Organometallic Chemistry,* **25**, 9-15 (2010).
14. J.L. Kelley, J.A. Linn, D.D. Bankston, C.J. Burchall, F.E. Soroko, B.R. Cooper, *J. Med. Chem.* 38, 3676 (1995).
15. G. Turan-Zitouni, Z.A. Kaplancikli, A. Özdemir, P. Chevallet, *Arch. Pharm. Chem. Life Sci.* 340, 586 (2007).
16. M.T.H. Tarafder, A. Kasbollah, N. Saravanan, K.A. Crouse, A.M. Ali, K.T. Oo, *J. Biochem. Mol. BioI. Biophys.* 6, 85 (2002).
17. G.H. Schmid, Organic Chemistry, New York, 1996.
18. F.A. Carry, Organic Chemistry', McGraw-Hill, 1992.
19. D.H. Brown, W.E. Smith, Enzyme Chemistry- impact and Applications, Chapmann and Hall, London, 1990.
20. K. Singh, M.S. Barwa, P. Tyagi, *Eur. J. Med. Chem.* 42, 394 (2007).
21. Nurşen Sarı, Nihat Pişkin, Hatice Öğütcü and Nurdan Kurnaz, Medicinal Chemistry Research, 2012, DOI: 10.1007/s00044-012-0039-5.
22. S. Chandra, J. Sangeetika, *J. Indian Chem. Soc.* 81, 203 (2004).
23. M.B. Ferrari, S. Capacchi, G. Pelosi, G. Reffo, P. Tarasconi, R. Albertini, S. Pinelli, P. Lunghi, *Inorg. Chim. Acta* 286, 134 (1999).
24. E. Canpolat, M. Kaya, *J. Coord. Chem.* 57, 1217 (2004).
25. M. Yildiz, B. Dulger, S.Y. Koyuncu, B.M. Yapici, *J. Indian Chem. Soc.* 81, 7 (2004)
26. H. Sakurai, H. Watanabe, H. Tamura, H. Yasui., R. Matsushita, J. Takada, *Inorg. Chim. Acta* **283**, 175 (1998); K. Kawabe, T. Suckuni, T. Inada, K. Yamato, M. Tadokoro, Y. Kojima, Y. Fujisawa, H. Sakurai, *Chem. Lett.* 1155 (1998)
27. H. Sakurai, K. Fujii, H. Watanabe, H. Tamura, *Biochem. Biophys. Res. Commun.* **214**,133 (1997).
28. S. Fujimoto, K. Fujii, H. Yasui, R. Mutsushita, J. Takada, H. Sakurai, J. *Clin. Biochem. Nutr.* **23**, 113 (1997); K. Kawabe, M. Tadokoro, Y. Kojima, Y. Fujisawa, H. Sakurai, *Chem. Lett.* 9(1998).
29. K. H. Thompson, J. H. McNeill and C. Orvig, *Chem. Rev.*, **99**, 2561 (1999).
30. T. E. McAlindon, M. P. La Valley, J. P. Gulin, D. T. Felson, *J. Am. Med. Asso.*, **283**, 1469 (2000); T. E.Towheed, T. P. Anastassiades, *J. Am. Med. Asso.*, **283**, 1483 (2000).
31. K. Pavelka, J. Gatterova, M. Olejarova, S. Machacek, G. Giacovelli, L. C. Rovatia, Intern. Med., **162**, 2113 (2002); B. Gyurcsik, L. Nagy, *Coord. Chem. Rev.*, **203**, 81 (2000).
32. M. Miyazaki, S. Nishimura, A. Yoshida, and N. Okubo, *Chem. Pharm. Bull.*, **27**, 532 (1979); M. T.Cocco, V. Onnis, G. Ponticelli, B. Meier, D. Rehder, E. Garribba and G. Micera, *J. Inorg. Biochem.*, **101**, 19 (2007).
33. Ya-Li Sang, Xue-Song Lin *J. Coord. Chem.*, **36**, 315 (2010)
34. P.G. Devi, S. Pal, R. Banerjee, D. Dasgupta, *J. Inorg. Biochem.* **101,** 127-137 (2007).

35. C. Dendrinou-Samara, L. Alevizopoulou, L. Iordanidis, E. Samaras, D. Kessissoglou, *J. Inorg. Bichem.* **89,** 89-96 (2002).
36. E. Bermejo, A. Castineiras, I. Garcia, D. X. West, "*Polyhedron* **22,** 1147-1154 (2003).
37. S. Chandra, L. K. Gupta, *Spectrochim. Acta Part A* **62,** 1089-1094 (2005).
38. K. S. Abou Melha, *J. Enzy. Inhib. And, Med. Chem.* **23,** 493-503 (2008).
39. M. Nath, S. Pokharia, R. Yadav, *Coord. Chem. Rev.* **215,** 99-149 (2001).
40. L. Casella, M. Gullotti, A. Pasini, M. Visca, *Inorg. Chim. Acta* **19C,** L9-L13 (1976).
41. A.I. El-Said, A.S.A. Zidan, M.S. El-Meligy, A.A.M. Aly, O.F. Mehammed, *Synth. React. Inorg. Met.-Org. Chem.* **30,** 1373-1392 (2000).
42. A.D. Jones, D.R. Williams, *Journal of Chemical Society A* 3159-3162 (1971).
43. I. Sakryan, E. Logoglu, S. Arslan, N. Sari, N. Sakryan, *BioMetals* **17,** 115-120 (2004).
44. J.R. Anacona, E. Bastardo, *Trans. Met. Chem.*, **24,** 478-480 (1999).
45. P. Clifford, S. Singh, J. Stjernsward, G. Klein, *Cancer Res.* **27(12)**, 2578-2615 (1967).
46. H. Schiff. *Annalen*, **131**, 118 (1864).
47. C. Baleizão, H. Garcia. *Chemical reviews*. **106(9)**:3987-4043 (2006).
48. R.H. Holm, J.R. Everett, and R.S. Chakravorty, *Inorganic Chemistry*, 7: 83-214 (1966).
49. M.J. Harvey, M. Proffitt, P. Wei, D.A. Atwood, *Chemical Communications*, **20(21)**, 2094-2095 (2001).
50. (a) F.D. Popp, *Journal of Organic Chemistry* **26 (5)** , 1566-1568 (1961). (b) F.D. , Popp, W. Kirsch, *Journal of Organic Chemistry*, **26 (10)** , pp. 3858-3860 (1961).
51. E.M. Hodnett, P.D. Mooney, *Journal of Medicinal Chemistry*, **13(4)**, 786 (1961).
52. J.R. Merchant, D.S. Chothia, *Journal of Medicinal Chemistry*, **13(2)**, 335-336 (1970).
53. James Ziegler, Theresa Schuerle, Lisa Pasierb, Crystal Kelly, Ashraf Elamin, Kelly A. Cole, and David W. Wright, *Inorg. Chem.*, **39 (16)**, 3731–3733 (2000).
54. Daniel E. Goldberg, Vijay Sharma, Anna Oksman, Ilya Y. Gluzman, Thomas E. Wellems and David Piwnica-Worms, *The Journal Biological Chemistry*, **272, (10)**, 6567–6572, (1997).
55. V. Sharma, D. Piwnica-Worms. *Chemical Reviews*, **99**, 2545-2560 (1999).
56. Kathryn E. Reinicke, Erik A. Bey, Melissa S. Bentle, JohnJ. Pink, Stephen T. Ingalls, Charles L. Hoppel, Rosana I.Misico, Gisela M. Arzac, Gerardo Burton, William G. Bornmann, Damon Sutton, Jinming G Ao, and David A. Boothman, *Clin Cancer Res*;**11**, 3055-3064 (2005).
57. J.W. Mo, B. Ogorevc, *Analytical Chemistry* **73 (6)**, 1196-1202 (2001).
58. H. L. Singh, *Phosphorus, Sulfur and Silicon* **184(7),** 1768-1778 (2009).
59. E. Garcia, B.R. Jacobson, Q. Hu, *Applied Physics Letters* **63 (7)**, 1002-1004 (1993).
60. P.G. Cozzi, *Chemical Society Reviews* **33 (7)**, 410-421 (2004).
61. J. Patole, D. Shingnapurkar, S. Padhye, C. Ratledge. *Bioorganic & Medicinal Chemistry Letters*, **16**, 1514-1517 (2006).
62. V.T Dao, M.K Dowd, M.T Martin, C. Gaspard, M. Mayer, R.J. Michelot, *European Journal of Medicinal Chemistry*, **39**, 619-624 (2004).

63. Khan A, Sarkar S, Sarkar D. *International Journal of Antimicrobial Agents*, **32**, 40-45 (2008).
64. M.S. Iqbal, A.H. Khan, B.A. Loothar, I.H. Bukhari. *Medicinal Chemistry Research*, **18**, 31-42 (2009).
65. P.G. Kulkarni, G.B. Avaji, Bagihalli, S.A Patil, P.S. Badami. *Journal of Coordination Chemistry* **62**, 481-492 (2009).
66. G. Puthilibai, S. Vasudevan, S.K. Rani, G. Rajagopal. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, **72**, 796-800 (2009).
67. P.G Avaji, C.H.V Kumar, S.A Patil, K.N. Shivananda, C. Nagaraju. *European Journal of Medicinal chemistry*, **2009** doi:10.1016/j.ejmech.2009.03.032 (2009).
68. G.B. Bagihalli, P.G. Avaji, S.A. Patil, P.S. Badami. *European Journal of Medicinal Chemistry* **43**, 2639-2649 (2008).
69. N. Chitrapriya, V. Mahalingam, L.C. Channels, M. Zeller, F.R. Fronczek, K. Natarajan *Inorganica Chimica Acta*, **361**, 2841–2850 (2008).
70. E. Keskioglu, A.B. Gunduzalp, S. Cete, F. Hamurcu, B. Erk. *Spectrochimica Acta Part A*, **70,** 634–640 (2008).
71. H. Katircioglu, Y. Beyatlı, B. Aslim, Z. Yuksekdag, T. Atici. *Internet Journal of Microbiology*, **2**, 2 (2006).
72. V.P. Daniel, B. Murukan, B.S. Kumari, K. Mohanan. *Spectrochimica Acta Part A*, **70**, 403–410 (2008).
73. M.S. Nair, R.S. Joseyphus. *Spectrochimica Acta Part A*, **70**, 749–753 (2008).
74. A.S. El-Tabl, F.A. El-Saied, W. Plass, A.N. Al-Hakimi. *Spectrochimica Acta Part A*, **71**, 90–99 (2008).
75. K. Shahid, S. Ali and S. Shazadi, *J. Coord. Chem.*, **62,** 2919-2926 (2009).
76. V. Sharma, A. Beatty, D.E. Goldberg, D. Piwnica-Worms. *Chemical Communication*, 2223-2224 (1997).
77. T.S.B. Baul, A. Paul, L. Pellerito, M. Scopelliti, P. Singh, P. Verma, A. Duthie, D. De Vos, E.R.T. Tiekink, *Investigational New Drugs*, **29**, 285-299 (2011)..
78. K.E. Erkkila, D.T. Odom, J.K. Barton. *Chemical Reviews*, **99**, 2777–2796 (1999).
79. C. Liu, M. Wang, T. Zhang, H. Sun. *Coordination Chemistry Reviews*, **248**, 147–168 (2004).
80. D.S. Sigman, A. Mazumder, D.M. Perrin, *Chemical Reviews*. **93**, 2295–2316 (1993).
81. K.J. Humphreys, K.D. Karlin, S.E. Rokita. *Journal of American Chemical Society*, **124**, 8055–8066 (2002).
82. M. Nath, H. Singh, G. Eng, X. Song, X. *Inorganic Chemistry Communications*, **14**, 1381-1385 (2011).
83. S.A. Tysoe, R. Kopelman, D. Schelzig. *Inorganic Chemistry, 38 (23)*, 5196–5197 (1999).
84. C. Liu, S. Yu, D. Li, Z. Liao, X. Sun, H. Xu. *Inorganic Chemistry*, **41 (4)**, 913–922 (2002).
85. A.C. Lim, J.K. Barton. *Biochemistry*, **32 (41)**, 11029-11034 (1993).

86. S. Dhar, M. Nethaji, A.R. Chakravarty. *Inorganic Chemistry*, **45**, 11043–11050 (2006).
87. M. Roy, S. Saha, A.K. Patra, M. Nethaji, A.R. Chakravarty. *Inorganic Chemistry*, **46**, 4368–4370 (2007).
88. A.T. Chaviara, E.E. Kioseoglou, A.A. Pantazaki, A.C. Tsipis, P.A. Karipidis, D.A. Kyriakidis, C.A. Bolos. *Journal of Inorganic Biochemistry*, **102**, 1749–1764 (2008).
89. E.V. Hackl, V.L. Galkin, Y.P. Blagoi. *International Journal of Biological Macromolecules*, **34**, 303-308 (2004).
90. K. Jiao, Q.X. Wang, W. Sun, F.F. Jian. *Journal of Inorganic Biochemistry*, **99**, 1369-1375 (2005).

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